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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/716,825	STEPHANOPOULOS ET AL.	
	Examiner	Art Unit	
	Amber D. Steele	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 September 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8-10 and 12-32* is/are pending in the application.

4a) Of the above claim(s) *2-4 and 12-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5,6 and 8-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

Status of the Claims

1. The amendment received on October 2, 2006 canceled claim 7.

The amendment to the claims received on September 20, 2007 amended claims 1, 8, and 9 and canceled claim 11.

Claims 1-6, 8-10, and 12-32 are currently pending.

Claims 1, 5-6, and 8-10 are currently under consideration.

Election/Restrictions

2. This application contains claims 12-32 drawn to inventions nonelected with traverse in the reply filed on October 2, 2006. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

3. Applicants' election without traverse of mRNA as the species of expression level in the reply filed on October 6, 2006 is reiterated. Claims 2-4 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on October 6, 2006.

Priority

4. The present application (10/716,825, filed November 18, 2003) claims status as a CIP of U.S. application 10/060,048 filed January 29, 2002 and claims benefit of U.S. provisional application 60/427,265 filed November 18, 2002.

5. The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, provisional Application No. 60/427,265, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. U.S. provisional application 60/427,265 does not teach the genes of Table 1.

However, this does not change the priority date of the claims. The claims presently have a priority date of January 29, 2002.

Invention as Claimed

6. A method for diagnosing an oral cancer in a patient comprising: (a) obtaining a biological sample from a patient, (b) determining the expression level of a plurality of genes associated with an oral cancer in the biological sample, thereby producing a test expression profile, and (c) comparing the test expression profile with at least one signature expression profile of the plurality of genes selected from Table 1 indicative of an oral cancer wherein if the test expression profile substantially matches a signature expression profile indicative of an oral cancer the patient has the oral cancer and variations thereof.

Please note: Table 1 refers to genes via accession number, gene name, chromosome location, and function. Therefore, any of the designations (i.e. accession number, gene name, chromosome location, and function) would read on the genes of Table 1.

Sequence Compliance

7. MPEP § 2422.02 states the following: "The requirement for compliance in 37 CFR 1.821(c) is directed to "disclosures of nucleotide and/or amino acid sequences." All sequence information, whether claimed or not, that meets the length thresholds in 37 CFR 1.821(a) is subject to the rules. In those instances in which prior art sequences are only referred to in a given application by name and a publication or accession reference, they need not be included as part of the "Sequence Listing," unless an examiner considers the referred to sequence to be "essential material," per MPEP § 608.01(p). However, if the applicant presents the sequence as a string of particular bases or amino acids, it is necessary to include the sequence in the "Sequence Listing," regardless of whether the applicant considers the sequence to be prior art. In general, any sequence that is disclosed and/or claimed as a sequence, i.e., as a string of particular bases or amino acids, and that otherwise meets the criteria of 37 CFR 1.821(a), must be set forth in the "Sequence Listing."

The genes listed in Table 1 and claimed (independent claim 1) are considered essential material. Therefore, the submission of a sequence listing, a CRF, and a statement that the sequence listing and the CRF are the same is required. Applicant is cautioned that no new matter may be added to the specification. Therefore, only sequences associated with the genes of Table 1 available at the time of filing may be submitted.

Withdrawn Objection

8. The objection to the disclosure regarding reference numbers 20 and 22 for Figure 2 is withdrawn in view of the amendment to the specification rece4ived on September 20, 2007.

Withdrawn Rejections

9. The rejection of claims 1, 5-6, and 8-11 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention regarding "point of care" is withdrawn in view of the claim amendments received on September 20, 2007.

10. The rejection of claim 10 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention regarding assaying biological samples including bone marrow aspirates, bone marrow biopsies, lymph node aspirates, and lymph node biopsies would be useful in diagnosing oral diseases is withdrawn in view of applicants arguments and the ability of oral cancer to metastasis. Thus, the limitations of claim 10 will be interpreted as encompassing metastatic oral cancer samples as well as non-metastatic oral cancer samples.

11. The rejection of claim 11 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention regarding HIV as an oral disease is withdrawn in view of the claim amendments received on September 20, 2007.

12. The rejection of claims 1, 5-6, and 8-11 under 35 U.S.C. 102(b) as being anticipated by Hillman et al. U.S. 6,121,019 issued September 19, 2000 is withdrawn in view of the amendments received on September 20, 2007 (i.e. Table 1).

New Rejection Necessitated by Amendment

Claim Rejections - 35 USC § 112

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 1, 5-6, and 8-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Independent claim 1 refers to the genes of Table 1. However, Table 1 refers to the genes by accession number, gene name, chromosome location, and function. Thus, it is not clear if the genes of Table 1 require a specific sequence, the entire gene sequence, a sequence associated with the accession number, a sequence associated with the gene name, an EST, etc. MPEP § 2173.05(s) states the following: Where possible, claims are to be complete in themselves. Incorporation by reference to a specific figure or table "is permitted only in exceptional circumstances where there is no practical way to define the invention in words and where it is more concise to incorporate by reference than duplicating a drawing or table into the claim. Incorporation by reference is a necessity doctrine, not for applicant's convenience." *Ex parte Fressola*, 27 USPQ2d 1608, 1609 (Bd. Pat. App. & Inter. 1993) (citations omitted). Furthermore, independent claim 1 requires comparing a test expression profile with a signature expression profile of the plurality of genes selected from Table 1. However, it is not clear from

the claims if all of the genes in Table 1 are required or only a subset of the genes of Table 1 (please also refer to claims 8-9).

15. Claims 8-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 8-9 recite the limitation "the plurality of genes" in line 2 of each respective claim. There is insufficient antecedent basis for this limitation in the claim. The plurality of genes selected from Table 1 is suggested.

Maintained Rejections

16. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Please note: the rejections may have been altered to reflect the claim amendments received on September 20, 2007.

Claim Rejections - 35 USC § 112

17. Claims 1, 5-6, and 8-10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications under the 35 USC 112, first paragraph "Written Description" requirement, Federal Register, Vol. 66, No. 4 pages 1099-1111, Friday January 5, 2001. This is a **written description** rejection.

Claim 1 is drawn to a method for diagnosing an oral cancer in a patient comprising (a) obtaining a biological sample from a patient, (b) determining the expression level of a plurality of genes associated with oral cancer (i.e. test expression profile), and (c) comparing the test expression profile with at least one signature expression profile of the plurality of genes selected form Table 1. The invention as claimed encompasses all known genes associated with all oral cancers, all genes which may potentially be associated with all oral cancers in the future, and any yet to be discovered oral cancers. It is noted that method step (b) requires determining the expression level of a plurality of genes (i.e. any genes) while only method step (c) requires the genes of Table 1. The claimed invention does not include any structural information regarding the genes of the test expression profile and refers to the genes of Table 1 via accession number, gene name, chromosome location, and function (i.e. sequences are not provided).

The specification teaches 45 genes (please refer to Table 1). In addition, the specification teaches that of the various genes analyzed utilizing the GeneChip® array only 30 of the genes were "downregulated" and 15 of the genes were "upregualted" in five patients with oral cancer wherein the specific type of oral cancer is not disclosed (please refer to pages 69 and 72-73). However, the claimed invention does not include any structural limitations regarding the genes. Table 1 refers to the genes by accession number, gene name, chromosome location, and function. Thus, one of skill in the art would not determine that applicants had possession of every sequence associated with every accession number, gene name, chromosome location, and function including the entire gene sequence, fragments of the gene sequence, all sequences associated with the accession number, all sequences associated with the gene name, all ESTs, etc. Further exacerbating the lack of written description is the lack of an association between

some of the accession numbers with any sequences or the association of the gene name with multiple sequences (i.e. HG3549-HT3751 and Wilm Tumor-Related Protein; HG2992-HT5186 and Beta-Hexosaminidase, Alpha; please refer to the NCBI printouts, 6 pages). Furthermore, the claimed invention does not teach how the genes can be utilized to diagnose oral disease (e.g. correlation of gene expression to disease; level of upregulation or downregulation expected in diseased samples, etc.). Therefore, one skilled in the relevant art would not reasonably conclude that the Applicants had possession of the invention as claimed since the structural limitations of the genes are not included in the claimed invention and diagnosis of oral cancer via the genes in Table 1 has not been established.

See Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was *in possession of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See page 1116.).

With the exception of analyzing an oral cancer sample for expression of the 45 gene names (i.e. not every sequence associated with each accession number, gene, chromosome, or function) as disclosed by the specification, the skilled artisan cannot envision the method of claim 1. In addition, it is noted that while the art recognizes certain genetic markers that may correlate to oral diseases a specific, definitive genetic marker for diagnosing oral diseases including oral cancer have not been recognized in the art. For example, (1) Rosas et al. (Cancer Research 61: 939-942, 2001) teach that gene expression levels may not be altered, but rather

methylation of the genes may be altered in head and neck tumors (i.e. only 23-56% of patients with head and neck primary tumors had hypermethylated genes; e.g. levels not conclusive for diagnostic purposes; please refer to abstract, Results, and Discussion sections), (2) Liao et al. (Oral Oncology 36: 272-276, 2000) teach that 62.5% of patients with oral squamous cell carcinoma were positive for p53 mutations while 18.52% of samples from healthy patients had p53 mutations (e.g. not conclusive for diagnostic purposes; please refer to abstract and Discussion section), and (3) Williams (Journal of Clinical Pathology 53: 165-172, 2000) teach that oral squamous carcinogenesis is a multistep process involving multiple genetic events wherein not all genetic events occur in all squamous oral carcinogenesis or similar genetic alteration may occur at different times (please refer to abstract and Conclusion section). Thus, while the art recognizes genetic markers that may correlate to oral diseases (e.g. associated with an oral disease or determining if a patient has a higher risk of having an oral disease), the art does not presently recognize one or more genetic markers that can be utilized to definitively diagnose oral diseases including oral cancer. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class wherein the specification provided only the bovine sequence.

Arguments and Response

18. Applicants' arguments directed to the rejection under 35 USC 112, first paragraph (written description), for claims 1, 5-6, and 8-10 were considered but are not persuasive for the following reasons.

Applicants contend that the specification amply teaches the claimed invention and provides working examples (pages 69-80) of the claimed invention particularly the genes of Table 1.

Applicants' arguments are not convincing for the reasons of record. Specifically, the genes of Table 1 are described by accession number, gene name, chromosome location, and function. Thus, one of skill in the art would not determine that applicants had possession of every sequence associated with every accession number, gene name, chromosome location, and function including the entire gene sequence, fragments of the gene sequence, all sequences associated with the accession number, all sequences associated with the gene name, all ESTs, etc. Further exacerbating the lack of written description is the lack of an association between some of the accession numbers with any sequences or the association of the gene name with multiple sequences (i.e. HG3549-HT3751 and Wilm Tumor-Related Protein; HG2992-HT5186 and Beta-Hexosaminidase, Alpha; please refer to the NCBI printouts, 6 pages). In addition, the working examples on pages 69-80 state that the "45 genes are strongly correlated with the appearance of malignancy in oral epithelium" (page 69,lines 9-10) and "the 45 genes...exhibit close association with oral cancer development" (page 72, lines 27-28) which would not be considered definitively diagnostic to one of skill in the art. In addition, it is noted that applicants

have tested a very small number of samples (i.e. five patients) in determining that the genes of Table 1 are "diagnostic".

19. Claims 1, 5-6, and 8-10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is a **scope of enablement** rejection.

There are many factors to consider when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any experimentation is "undue". These factors include, but are not limited to:

1. The breadth of the claims;
2. The nature of the invention;
3. The state of the prior art;
4. The level of skill in the art;
5. The level of predictability in the art;
6. The amount of direction provided by the inventor;
7. The presence or absence of working examples;
8. The quantity of experimentation necessary needed to make or use the invention based on the disclosure.

See *In re Wands* USPQ 2d 1400 (CAFC 1988):

The breadth of the claims and the nature of the invention:

The presently claimed invention is drawn to a method for diagnosing an oral cancer in a patient comprising: (a) obtaining a biological sample, (b) determining the expression level of a plurality of genes associated with an oral cancer in the biological sample, thereby producing a test expression profile, and (c) comparing the test expression profile with at least one signature expression profile of the plurality of genes selected from Table 1 indicative of an oral cancer and variations thereof. The present claims do not provide any structural limitations regarding the genes in the test expression profile and do not provide any structural information regarding the genes of Table 1. Table 1 refers to the genes by accession number, gene name, chromosome location, and function. Thus, the genes of Table 1 are associated with multiple sequences based on the association of multiple sequences with accession numbers, gene names, chromosome locations, and functions (i.e. entire gene sequence, fragments of the gene sequence, all sequences associated with the accession number, all sequences associated with the gene name, all ESTs, etc.). Accordingly, the claims encompass all known and unknown genes and all known and unknown expression profiles (i.e. test expression profile) and multiple sequences based on the association of multiple sequences with accession numbers, gene names, chromosome locations, and functions (i.e. entire gene sequence, fragments of the gene sequence, all sequences associated with the accession number, all sequences associated with the gene name, all ESTs, etc.).

While the presently claimed method is enabled for screening biological samples for gene expression, the intended use as a means for diagnosing oral cancer is not enabled. The present specification merely states that of the various genes analyzed via GeneChip® array, the samples from five oral cancer patients (type, stage, etc. not specified) varied in 45 genes wherein 30

genes were "downregulated" and 15 of genes were "upregualted" (please refer to pages 69 and 72-73). The specification does not provide information regarding the level of upregualtion or downregulation compared to control (e.g. normal, noncancerous sample). Accordingly, the claim scope is unduly broad with respect to encompassed genes and expression profiles.

The state of the prior art and the level of predictability in the art:

Diagnosis of oral cancer via altered gene expression is highly unpredictable, particularly in humans. Rosas et al. (Cancer Research 61: 939-942, 2001) teach that gene expression levels may not be altered, but rather methylation of the genes and only 23-56% of patients with head and neck primary tumors had hypermethylated genes (e.g. levels not conclusive for diagnostic purposes; please refer to abstract, Results, and Discussion sections). Liao et al. (Oral Oncology 36: 272-276, 2000) teach that 62.5% of patients with oral squamous cell carcinoma were positive for p53 mutations while 18.52% of samples from healthy patients had p53 mutations (e.g. not conclusive for diagnostic purposes; please refer to abstract and Discussion section). Furthermore, Williams (Journal of Clinical Pathology 53: 165-172, 2000) teach that oral squamous carcinogenesis is a multistep process involving multiple genetic events wherein not all genetic events occur in all squamous oral carcinogenesis or similar genetic alteration may occur at different times (please refer to abstract and Conclusion section). Therefore, the level of predictability in the art is dependent on many factors including data interpretation, statistical analysis, animal models (e.g. wherein animal knockouts could provide more definitive evidence), long-term studies (e.g. following patients throughout course of disease to determine if gene expression is altered), etc. While finding genetic markers to accurately diagnose oral cancer is important, the state of the art requires vast amounts of data including correlation of the gene to

cancer with high probability, potentially finding one or more genetic markers for each oral cancer, detailed statistical analysis of data, etc. In addition, a showing that the genetic markers are specific for oral cancer and modulation is not associated with other diseases is required.

The level of skill in the art:

The level of skill would be high, most likely at the Ph.D. level.

The amount of direction provided by the inventor and the existence of working examples:

There are no specific examples directed to the intended use language of the presently claimed invention (i.e. diagnosing oral cancer in patients), nor is there any information provided regarding correlating the altered gene expression data provided in the specification and diagnosing oral cancer. The specification contains only cursory statements that various genes are "down" or "up" in cancer (please refer to Table 1).

The quantity of experimentation needed to make or use the invention based on the content of the disclosure:

In light of the unpredictability surrounding the claimed subject matter, the undue breadth of the claimed invention's intended use, and the lack of adequate guidance, one wishing to practice the presently claimed invention would be unable to do so without engaging in undue experimentation. One wishing to practice the presently claimed invention would have to facilitate clinical studies with large numbers of patients suffering from each known oral cancer and screen the entire genome to determine if any genes may be correlated to cancer, determine which sequences are relevant to the genes listed in Table 1, follow patients for years to determine if gene expression changes during the course of cancer, provide detailed statistical analysis of the data to limit potential false positives/negatives, etc.

Arguments and Response

20. Applicants' arguments directed to the rejection under 35 USC 112, first paragraph (enablement), for claims 1, 5-6, and 8-10 were considered but are not persuasive for the following reasons.

Applicants contend that including the limitation of Table 1 negates the enablement rejection.

Applicants' arguments are not convincing for the reasons of record. Specifically, the genes of Table 1 are described by accession number, gene name, chromosome location, and function. Thus, it is not clear which sequences are to be utilized in diagnosing oral cancer since Table 1 relates to multiple sequences which may be correlated to the accession number, gene name, chromosome location, and function including the entire gene sequence, fragments of the gene sequence, all sequences associated with the accession number, all sequences associated with the gene name, all ESTs, etc. In addition, some accession numbers are not presently correlated with any sequences or the gene name is associated with multiple sequences (i.e. HG3549-HT3751 and Wilm Tumor-Related Protein; HG2992-HT5186 and Beta-Hexosaminidase, Alpha; please refer to the NCBI printouts, 6 pages). In addition, the working examples on pages 69-80 state that the "45 genes are strongly correlated with the appearance of malignancy in oral epithelium" (page 69,lines 9-10) and "the 45 genes...exhibit close association with oral cancer development" (page 72, lines 27-28). However, pages 69-80 of the present specification also caution that diagnosis requires (1) determining which genes are relevant to disease and (2) determining a gene pattern that is a marker of a physiological state, but also questions whether the patterns can be utilized to diagnose cells or tissue samples (please refer to

the paragraph spanning pages 69-70). In addition, it is noted that applicants have tested a very small number of samples (i.e. five patients) in determining that the genes of Table 1 are "diagnostic".

21. Claims 1, 5-6, and 8-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. One of ordinary skill in the art would not be able to determine the scope of the presently claimed invention. The phrase "signature expression profile" is indefinite. For example, is a signature expression profile from a patient known to have an oral cancer, a "normal" donor, etc.; does the signature expression profile have 1, 2, 4, 8, 16, 32, etc. genes; is the signature expression profile simply the results in Table 1; etc.?

Arguments and Response

22. Applicants' arguments directed to the rejection under 35 USC 112, second paragraph (indefinite), for claims 1, 5-6, and 8-10 were considered but are not persuasive for the following reasons.

Applicants contend that the signature expression profile is "indicative of an oral cancer" and the genes are "selected from Table 1". In addition, applicants state that the specification teaches the following: "Applicants have discovered a set of genes that are differentially expressed in oral cancer cells versus normal cells. Applicants have shown that the expression profile of this set of genes is indicative of oral cancer, and as such, constitutes a signature expression profile of oral cancer. Thus, measuring expression levels of these genes in a sample cell population allows for the type and tumor stage of the cells in the sample to be determined"

(see, e.g., page 5, lines 5-10; and working examples). Further, the specification describes that the signature expression profile may be from either the 45 genes in Table 1 or a subset of the 45 genes in Table 1 (see, e.g., page 12, lines 5- 18). In light of the teachings of the specification, the expression "signature expression profile" is not ambiguous to one of skill in the art.

Applicants' arguments are not convincing for the reasons of record and because it is not clear if the signature expression profile as claimed requires all 45 genes or a subset of the genes and if a subset of genes which subset in Table 1 would still be able to diagnose oral cancer? In addition, it is not clear from the claims if the signature expression profile must exactly match the results found in Table 1 (i.e. the results of Table 1 are the signature expression profile) or if a new signature expression profile is required for each patient (i.e. an expression profile from non-cancerous tissue of the same patient being diagnosed which may have different results from the results in Table 1 or an expression profile from a patient known to have oral cancer).

Claim Rejections - 35 USC § 102

23. Claims 1, 5-6, and 8-10 are rejected under 35 U.S.C. 102(e) as being anticipated by Katz et al. U.S. Patent 6,797,471 filing date of August 6, 2001 and effective filing date of August 4, 2000.

For present claim 1, Katz et al. teach methods of identifying a subject at risk for developing smoking related cancers including obtaining a biological sample, determining expression levels of genes, and comparing to controls (e.g. signature expression profile; please refer to the entire specification particularly abstract; Figures 1-2 and 10-12; columns 3-6 and 8-21; claims 1-21). In addition Katz et al. teach utilizing genes from chromosomes 2, 3 (specifically 3p21.3), 5, 9, 10 (specifically 10q22), 17, 18, and 22 (i.e. genes of Table 1

associated with chromosomes 2, 3, 5, 9, 10, 17, 18, and 22 including fiberblast growth factor 8, KIAA0089, urokinase plaminogen activator, deoxyribonuclease 1-like 3, cytochrome P4502C9 subfamily IIC, diazepam binding inhibitor, cytochrome C oxidase subunit Vb, IL-8Rβ, transcription factor 20, KIAA-172, cathepsin L, aldehyde dehydrogenase 10, and lysophospholipase like; please refer to the entire specification particularly the abstract, column 1, lines 56-67; column 2, lines 1-57; column 8, lines 56-67).

For present claim 5, Katz et al. teach determining mRNA expression (please refer to the entire specification particularly column 16, lines 32-40; column 18, lines 35-54).

For present claim 6, Katz et al. teach isolating nucleic acids from the samples (please refer to the entire specification particularly column 14, lines 66-67; column 15, lines 1-4).

For present claim 8, Katz et al. teach mouth cancer, genes from chromosomes 3 and 10 particularly sections 3p21.3 and 10q22, genomic libraries, biomarkers, arrays, chips (e.g. over 45 genes; please refer to the entire specification particularly column 3, lines 1-28; column 5, lines 50-60; column 6, lines 6-25; column 11, lines 10-67; column 12, lines 59-67; column 13; column 19, lines 55-67; columns 20-21). In addition Katz et al. teach utilizing genes from chromosomes 2, 3 (specifically 3p21.3), 5, 9, 10 (specifically 10q22), 17, 18, and 22 (i.e. genes of Table 1 associated with chromosomes 2, 3, and 10 including fiberblast growth factor 8, KIAA0089, urokinase plaminogen activator, deoxyribonuclease 1-like 3, cytochrome P4502C9 subfamily IIC, diazepam binding inhibitor, cytochrome c oxidase subunit Vb, IL-8Rβ, transcription factor 20, KIAA-172, cathepsin L, aldehyde dehydrogenase 10, and lysophospholipase like; please refer to the entire specification particularly the abstract, column 1, lines 56-67; column 2, lines 1-57; column 8, lines 56-67).

For present claim 9, Katz et al. teach mouth cancer and genes including RPL14, CD39L3, PMGM, GC20, and PTEN (e.g. subset; please refer to the entire specification particularly column 3, lines 1-28; column 4, lines 37-46; column 6, lines 6-25). In addition Katz et al. teach utilizing genes from chromosomes 2, 3 (specifically 3p21.3), 5, 9, 10 (specifically 10q22), 17, 18, and 22 (i.e. genes of Table 1 associated with chromosomes 2, 3, and 10 including fiberblast growth factor 8, KIAA0089, urokinase plaminogen activator, deoxyribonuclease 1-like 3, cytochrome P4502C9 subfamily IIC, diazepam binding inhibitor, cytochrome c oxidase subunit Vb, IL-8Rβ, transcription factor 20, KIAA-172, cathepsin L, aldehyde dehydrogenase 10, and lysophospholipase like; please refer to the entire specification particularly the abstract, column 1, lines 56-67; column 2, lines 1-57; column 8, lines 56-67).

For present claim 10, Katz et al. teach biological samples including tissue and fine needle aspirations (please refer to the entire specification particularly column 3, lines 21-28; column 14).

Therefore, the presently claimed invention is anticipated by the teachings of Katz et al.

Arguments and Response

24. Applicants' arguments directed to the rejection under 35 USC 102 (e) as being anticipated by Katz et al. U.S. Patent 6,797,471 for claims 1, 5-6, and 8-10 were considered but are not persuasive for the following reasons.

Applicants contend that Katz et al. does not teach a signature expression profile of the plurality of genes selected from Table 1.

Applicants' arguments are not convincing since the teachings of Katz et al. anticipate the method of the instant claims. Katz et al. teach utilizing genes from chromosomes 2, 3

(specifically 3p21.3), 5, 9, 10 (specifically 10q22), 17, 18, and 22 (i.e. genes of Table 1 associated with chromosomes 2, 3, 5, 9, 10,.17, 18, and 22 including fiberblast growth factor 8, KIAA0089, urokinase plaminogen activator, deoxyribonuclease 1-like 3, cytochrome P4502C9 subfamily IIC, diazepam binding inhibitor, cytochrome C oxidase subunit Vb, IL-8Rβ, transcription factor 20, KIAA-172, cathepsin L, aldehyde dehydrogenase 10, and lysophospholipase like; please refer to the entire specification particularly the abstract, column 1, lines 56-67; column 2, lines 1-57; column 8, lines 56-67).

25. Claims 1, 5-6, and 8-10 are rejected under 35 U.S.C. 102(e) as being anticipated by Warrington et al. U.S. Patent 7,108,969 filing date of September 10, 2001 and effective filing date of September 8, 2000.

For present claim 1, Warrington et al. teach methods for monitoring gene expression profiles associated with oral cancer comprising obtaining a biological sample, determining, determining expression levels of genes, and comparing to controls (e.g. signature expression profile; please refer to the entire specification particularly abstract; Figures 1A, 1B, 2A, 2B, 2C, 3-6, 7A-7K; columns 2-13; Examples I-IV; claims 1-19). In addition, Warrington et al. teach accession numbers X76029, U34252, M69177, X02419, X78932, U46689, Y09616, M57731, Z29083, U18934, J04469, M11147, D13643, M61855, U67963, X07695, D43968, D42047, M34309, M14200, S45630, U56814, X87241, D79994, M30818, U06643, U24577, X15183, and X12451 among others (i.e. genes of Table 1; please refer to Figures 2A, 2B, 2C, 2D, 3, 6, 7A-7K).

For present claim 5, Warrington et al. teach determining mRNA expression (please refer to the entire specification particularly column 6, lines 31-54; column 7, lines 29-43; Example II).

For present claim 6, Warrington et al. teach isolation of nucleic acids from samples (please refer to the entire specification particularly column 7, lines 29-43; Example I).

For present claim 8, Warrington et al. teach oral cancer, 56 genes which are upregulated or downregulated, more than 45 genes, and microarrays (please refer to the entire specification particularly Figures 2C, 2D, and 7A-7K; column 2; Example II). In addition, Warrington et al. teach accession numbers X76029, U34252, M69177, X02419, X78932, U46689, Y09616, M57731, Z29083, U18934, J04469, M11147, D13643, M61855, U67963, X07695, D43968, D42047, M34309, M14200, S45630, U56814, X87241, D79994, M30818, U06643, U24577, X15183, and X12451 among others (i.e. genes of Table 1; please refer to Figures 2A, 2B, 2C, 2D, 3, 6, 7A-7K).

For present claim 9, Warrington et al. teach oral cancer, 39 genes, gene subsets (please refer to the entire specification particularly Figures 2A, 2B, 2C, 2D, 6, 7A-7K; column 2). In addition, Warrington et al. teach accession numbers X76029, U34252, M69177, X02419, X78932, U46689, Y09616, M57731, Z29083, U18934, J04469, M11147, D13643, M61855, U67963, X07695, D43968, D42047, M34309, M14200, S45630, U56814, X87241, D79994, M30818, U06643, U24577, X15183, and X12451 among others (i.e. genes of Table 1; please refer to Figures 2A, 2B, 2C, 2D, 3, 6, 7A-7K).

For present claim 10, Warrington et al. teach biological samples including tissue, blood (e.g. serum), and fine needle biopsy (e.g. aspirates; please refer to the entire specification particularly column 7, lines 29-57).

Therefore, the presently claimed invention is anticipated by the teachings of Warrington et al.

Arguments and Response

26. Applicants' arguments directed to the rejection under 35 USC 102 (e) as being anticipated by Warrington et al. U.S. Patent 7,108,969 for claims 1, 5-6, and 8-10 were considered but are not persuasive for the following reasons.

Applicants contend that Warrington et al. does not teach a plurality of genes selected from Table 1.

Applicants' arguments are not convincing since the teachings of Warrington et al. anticipate the method of the instant claims. Warrington et al. teach accession numbers X76029, U34252, M69177, X02419, X78932, U46689, Y09616, M57731, Z29083, U18934, J04469, M11147, D13643, M61855, U67963, X07695, D43968, D42047, M34309, M14200, S45630, U56814, X87241, D79994, M30818, U06643, U24577, X15183, and X12451 among others (i.e. genes of Table 1; please refer to Figures 2A, 2B, 2C, 2D, 3, 6, 7A-7K).

Conclusion

27. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Future Communications

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amber D. Steele whose telephone number is 571-272-5538. The examiner can normally be reached on Monday through Friday 9:00AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Doug Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

ADS
November 14, 2007

/Jon D. Epperson/
Primary Examiner, AU 1639

Notice to Comply	Application No. 10716825	Applicant(s) STEPHANOPOULOS ET AL.
	Examiner Amber D. Steele	Art Unit 1639

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set in the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☒ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: please refer to the attached Office action.

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", **as well as an amendment specifically directing its entry into the application**.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

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